Effect of Noncontact Normothermic Wound Therapy on the Healing of Neuropathic (Diabetic) Foot Ulcers: An Interim Analysis of 20 Patients

Oscar M. Alvarez, PhD,[1] Roisin S. Rogers, RN, MSN, CWCN,[1,2] Juanita G. Booker, RN, BSN,[1,2] and Mayank Patel, MD[1]

This is the interim analysis of a prospective, randomized, controlled study comparing diabetic foot ulcer healing in patients being treated with either noncontact normothermic wound therapy (Warm-UP; Augustine Medical Inc. Eden Prairie, MN) applied for 1 hour 3 times daily until healing or 12 weeks, or standard care (saline-moistened gauze applied once a day). Surgical debridement and adequate foot off-loading was provided to both groups. Evaluations were performed weekly and consisted of acetate tracings, wound assessment, and serial photography. Twenty patients have completed the trial and both treatment groups were distributed evenly (N = 10). Ulcers treated with noncontact normothermic wound therapy had a greater mean percent wound closure than control-treated ulcers at each evaluation point (weeks 1–12). After 12 weeks, 70% of the wounds treated with noncontact normothermic wound therapy were healed compared with 40% for the control group. In this subset of patients there have been no adverse events associated with noncontact normothermic wound therapy. (The Journal of Foot & Ankle Surgery 42(1):30–35, 2003)

Key words: wound healing, diabetic foot ulcers, neuropathic ulcers

The warming of wounds to aid in healing has been practiced since the time of Hippocrates (460–380 BC). The Hippocratic theory (which talks of wounds as diseases) explains, “If a wound is chilled, the exposed blood vessels (venules) caught cold and convulsed. A convulsing venule around the wound would develop spasms, attract blood, become soaked with it and decay”(1–3).

Today, there is general belief that wound healing is improved if wounds are maintained in an environment that is warm, moist, and clean. In acute wounds, moist wound healing impedes the development of a crust and allows for epithelial cells to migrate more quickly over the wound (4–6). In chronic wounds, fibroblast, macrophages, endothelial, and other cells involved in the healing process seem to prefer a moist environment (7, 8). Warmth around the wound is thought to cause dilation of the local blood vessels and thus improve the delivery of oxygen, growth factors, and other nutrients to the wound (9, 10). A clean environment assists in protecting the wound from infection (11).

A wound healing therapy system has been developed that provides a warm, moist, and clean environment to the wound. Noncontact normothermic wound therapy (NNWT) (Warm-UP; Augustine Medical Inc., Eden Prairie, MN) is based on the premise that most tissues and organs function best when they are maintained at a relatively constant normal body temperature (normothermia) of 37°C ± 1°C. NNWT is designed to deliver gentle heat through a noncontact, semi-occlusive, moisture-retentive wound cover (dressing). The system warms the wound and the surrounding skin to core body temperature near 37°C.

There is a growing body of evidence that warming wounds with moist heat improves healing (12–15). Several possible mechanisms have been proposed, including biochemical modification of wound fluid (16), improved transcutaneous oxygen transport (17), greater collagen deposition (18), and stimulation of fibroblast growth (19).

Skin surface temperatures are lower than core body temperatures (20) and the temperature of the skin on the extremities is lower than on the face and the trunk (20, 21). In addition, depending on the air temperature, the surface

From the [1]University Wound Care Center, Bronx, NY; and [2] The Visiting Nurse Service of New York, New York, NY. Address correspondence to: Oscar M. Alvarez, PhD, University Wound Care Centers, 3175 East Tremont Ave., Bronx, NY 10461. e-mail: oalvarez@comcast.net.

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temperature of the feet can range between 26°C and 34°C and the greatest variability in skin surface temperatures are observed on the feet (20). Therefore, if normothermic wound therapy is effective for skin wounds on the body trunk it should have an even greater effect on the healing of wounds on the plantar surface of the feet.

To test this hypothesis, we chose to study the healing of diabetic neuropathic foot ulcers. The potential for faster wound healing in this patient population could lead to a reduction in the incidence of (wound and bone) infection, thereby resulting in fewer amputations.

Materials and Methods

Study Design and Patient Population

This is the interim analysis of an ongoing, prospective, randomized, parallel-group, open-label, controlled trial to evaluate the efficacy of NNWT for the healing of diabetic neuropathic foot ulcers. Eligible patients older than 18 years were entered into the study after an institutional review board approval. Informed consent was obtained. Patients were assigned randomly to receive either NNWT or the control regimen of saline dressings according to a computer-generated randomization schedule. The patients were followed up for 12 weeks for analysis of efficacy end points.

Twenty patients were treated; for statistical analysis, all 20 patients who met inclusion and exclusion criteria were evaluated, with 10 patients randomized to NNWT and 10 patients to the control group. All wounds were diabetic neuropathic foot ulcers defined as follows: an ulcer on the plantar surface of the foot in a patient with a diagnosis of type 1 or 2 diabetes mellitus. The target ulcer must have been secondary to peripheral neuropathy in a patient with adequate arterial circulation (ankle-to-brachial index, >0.7 and palpable pulses). The ulcer had to extend through the dermis and into subcutaneous tissue (granulation tissue may be present), but without exposure of muscle, tendon, bone, or joint capsule. Exclusion criteria were as follows: clinical signs of infection, osteomyelitis, cellulitis, uncontrolled diabetes, and any other clinically significant medical conditions that would impair wound healing inclusive of renal, hepatic, hematologic, neurologic, or immunologic disease. Patients taking corticosteroids, immunosuppressive agents, radiation, or chemotherapy within 1 month before entry into the study also were excluded.

Debridement Procedures

Initial aggressive sharp debridement of the ulcer was performed at the initial evaluation day 0. This debridement included removal of necrotic tissue, elimination of undermining, and wound margins excised to healthy bleeding tissue. At each weekly follow-up visit, minor debridement was performed to remove callus surrounding the ulcer, eliminate undermining, and expose the wound margins. Hydrotherapy or other pressurized mechanical methods of wound debridement were not performed. Chemical or enzymatic debridement ointments were not used at any time throughout the study.

Off-Loading and Therapeutic Sandals

All patients were fitted with a therapeutic healing sandal with customized plastizote inserts (cut out in the area over the ulcer) to redistribute pressure away from the ulcer. Patients were instructed to avoid bearing weight on the affected foot and were given crutches and a wheelchair.

NNWT System

The NNWT system shown in Figure 1 is a noncontact thermal wound care system designed to provide a wound environment that maintains wound and surrounding skin surface temperature at 37°C. NNWT consists of a wound cover that serves as the primary wound dressing, a heating element or warming card, and a power supply. The wound cover consists of 2 layers of high–moisture, vapor-permeable polyurethane film supported by and attached to a donut-shaped, open-cell foam pad that is coated with a medical-grade adhesive. The center transparent window portion of the wound cover is a 2-layered pocket that houses the warming card. The window is positioned directly over the wound and allows for visualization of the wound when the warming card is not inserted in the pocket. The warming card is the heating element. It is a flat, thin, reusable, resistant heater that connects to the power supply. The warming card does not come in contact with the skin because it remains suspended approximately 1 cm from the wound bed by the wound cover. The power supply is the control unit and automatically maintains the temperature of the heating element at 38°C. The cordless power supply contains a rechargeable battery, measures 15 cm $\times$ 10 cm, is 1.5-cm thick, and weighs 12.5 ounces.

The wound cover was applied over the ulcer and served as the primary dressing. The foot was then bandaged with a bulky gauze bandage and covered with an elastic rib-knit stockinet. The wound cover was changed once daily unless it became saturated with exudate or strike-through occurred. Warming treatments were performed 3 times daily for 1 hour each time, waiting at least 1 hour between warming sessions. Treatment was provided until the wound healed or for a maximum period of 12 weeks.

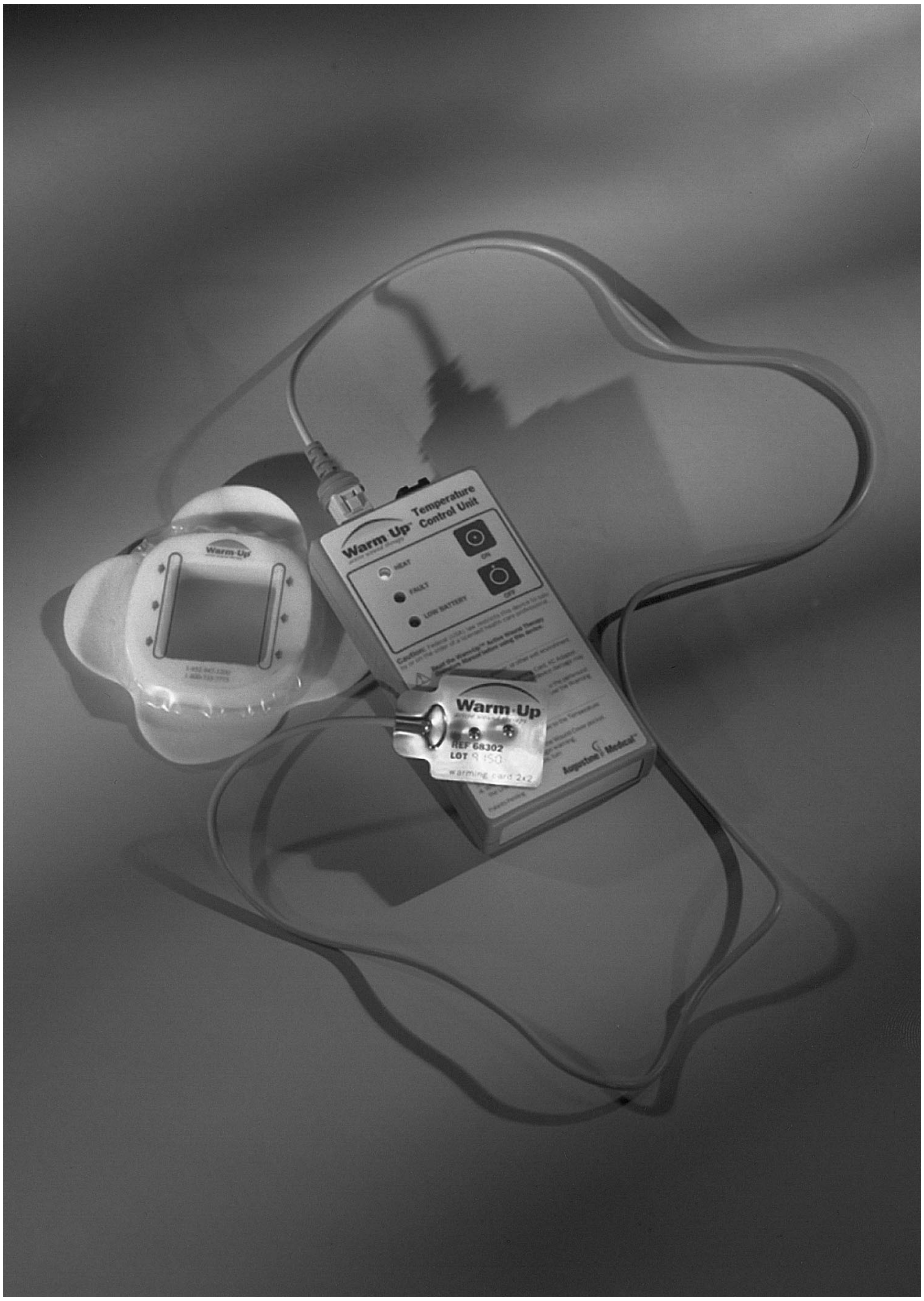

FIGURE 1 NNWT system consists of an adhesive wound chamber, a warming card, and a temperature control unit. It is applied for 1 hour 3 times daily.

Control Dressings

Patients randomized to the control group received standard wound care, consisting of weekly debridement and moist to moist saline gauze dressings (the gauze was not allowed to dry). The wound was rinsed with normal saline, covered with saline-moistened fine mesh gauze, followed by dry gauze sponges, bandaged with rolled bulky gauze, and covered with an elastic rib-knit stockinet. Wound dressings were changed once daily.

Study Evaluations

On randomization, after debridement and before treatment, patients were evaluated (baseline, day 0). Baseline

evaluation consisted of a clinical wound assessment including overall wound condition, erythema, edema, wound margins (undermining), and amount and type of granulation and exudate. The size of the wound was determined by computerized planimetry of surface tracings made with an acetate transparent film. The wounds were photographed after debridement and before dressing application. At each weekly evaluation, the wound was assessed for closure. Wound closure was defined as full epithelialization of the wound with absence of drainage and no longer needing a dressing. After light debridement the wound was traced, photographed, and clinically graded. Clinical assessment included signs of infection, cutaneous undermining, amount of granulation, and amount of drainage.

A record was maintained of the patient's fasting blood sugar level and the diary was checked to verify that radiant heat therapy was applied for 1 hour 3 times daily. Concurrent medication use was updated and both intercurrent and adverse events were recorded.

The primary efficacy end points were proportion of wounds healed by 12 weeks and time to complete wound closure. The secondary end point was rate of wound healing (percent reduction in wound surface area).

Statistical Analysis

Summarized numeric parameters were evaluated using Student *t* test after testing for normality. A χ^2 test was used to detect significant differences between treatment groups in the proportion of patients who healed (22). Values representing percent reduction in wound size also were compared using Student *t* test for testing the difference between the means of 2 independent samples (23). Significant differences were evaluated using an α level of .05.

Results

There were no significant differences between the NNWT and control treatment groups in patient demographics and baseline ulcer size (Table 1). Treatment with the NNWT system was reported as "easy to use" by the patients. Overall, there was excellent compliance with the use of NNWT (an average of 2.7 warming sessions were performed each day). The application of noncontact normothermic wound therapy was not associated with pain or discomfort. No adverse events were reported with either treatment. The most common intercurrent event was skin maceration of the area surrounding the wound in the NNWT group. Skin maceration was observed in 4 of the 10 patients.

Treatment with NNWT had a greater mean percent wound closure than control-treated ulcers at each evaluation point (Fig. 2). Although the differences were notable and displayed a trend favoring NNWT, the differences in healing rate were not statistically significant (P = .085 at week 2, P = .059 at week 4, P = .062 at week 6, P = .064 at week 8, P = .054 at week 10, and P = .074 at week 12. Ulcer photographs showing the sequence of healing in a patient treated with NNWT are shown in Figure 3.

TABLE 1 Patient characteristics on admission

Variable	NNWT N = 10	Control N = 10
Sex		
F, %	40	60
M, %	60	40
Mean age	61	53
Range	38–75	47–78
Ulcer area (mean, mm^2)	346	216
Ulcer location		
(Forefoot, %)	70	80
(Other, %)	30	20
More than 1 ulcer, %	40	10
Hx of nonhealing,		
<1 y, %	70	90
1–3 y, %	30	10
Diabetes		
Type I	10	0
Type II	80	90
Insulin dependent, %	50	40

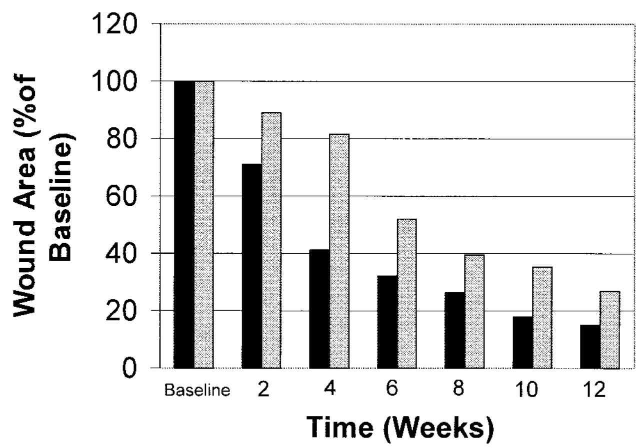

FIGURE 2 Mean percent wound area of ulcers treated with NNWT and control. (■) NNWT; (□) control.

After 6 weeks, 30% of the ulcers treated with NNWT had healed compared with 10% for the control group (P = .11). After 12 weeks 70% of the ulcers treated with NNWT healed compared with 40% for the control group (P = .069; Fig. 4).

Discussion

The treatment of diabetic foot ulcers with a controlled level of warmth and moisture provided by NNWT resulted in a greater proportion of wounds healed by 12 weeks and a greater mean percent wound closure over time. The dif-

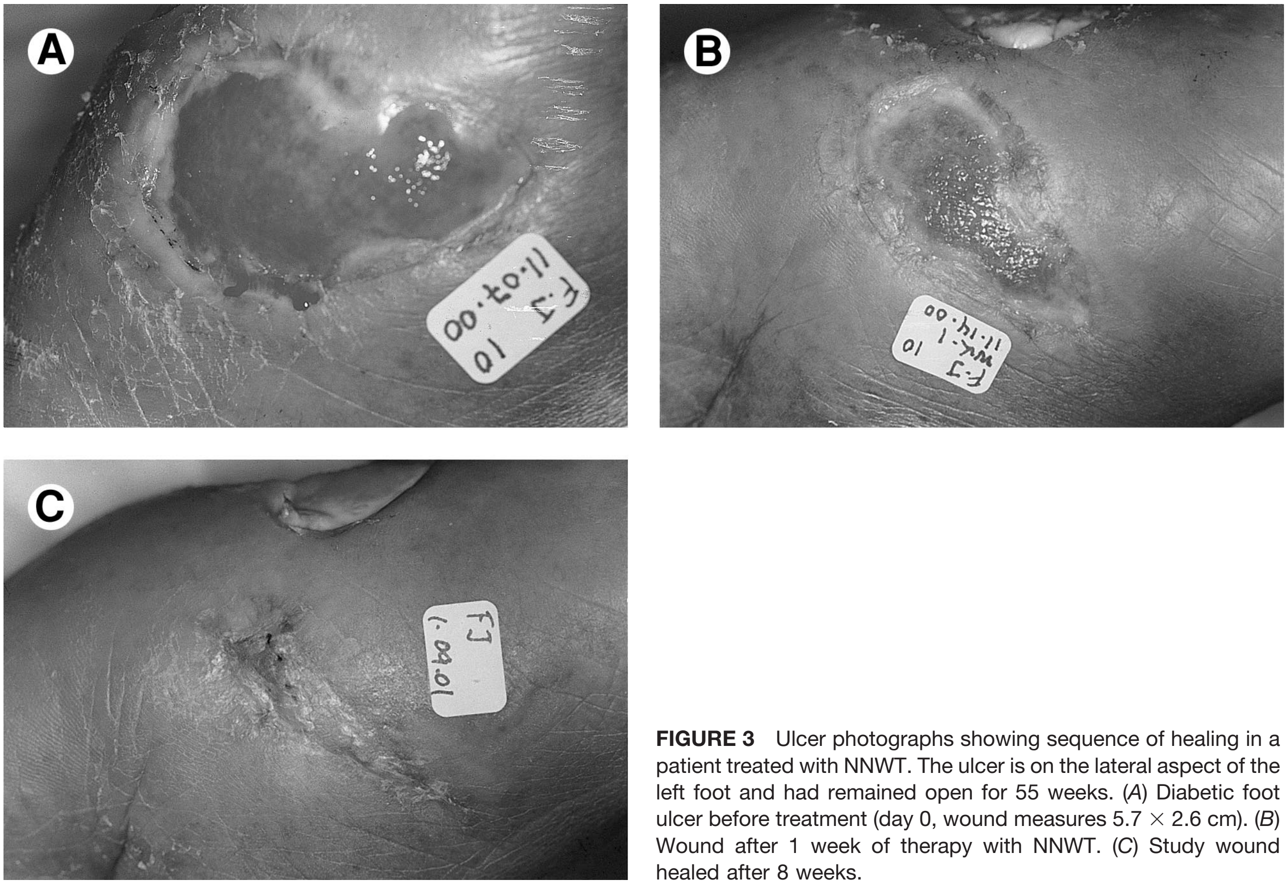

FIGURE 3 Ulcer photographs showing sequence of healing in a patient treated with NNWT. The ulcer is on the lateral aspect of the left foot and had remained open for 55 weeks. (*A*) Diabetic foot ulcer before treatment (day 0, wound measures 5.7 $\times$ 2.6 cm). (*B*) Wound after 1 week of therapy with NNWT. (*C*) Study wound healed after 8 weeks.

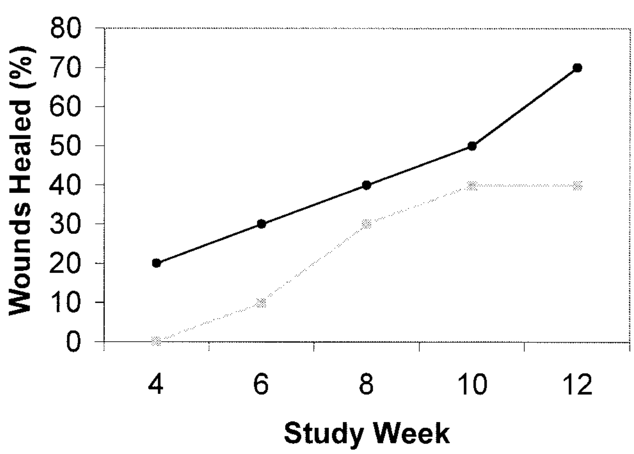

FIGURE 4 Effect of NNWT on the proportion of wounds healed. (●) NNWT; (▢) control.

ferences in healing were not statistically significant because of the small sample size in each treatment group (N = 10).

The most feasible explanation for the improved healing of diabetic foot ulcers treated with NNWT is the result of increased perfusion of blood (21) combined with an increase in oxygen tension (17) owing to vasodilation of cutaneous blood vessels. Although these parameters were not measured in our studies they have been reported in the literature. Rabkin and Hunt showed that local heat increases blood flow and oxygen tension in wounds in a linear fashion (10). An increase of 5.6–22.5 mm Hg oxygen tensions can be expected per 1°C increase in skin surface temperature. Ikeda et al. (17) showed that warming to 38°C with NNWT significantly increases oxygen tensions in subcutaneous tissue. Warmer tissues have greater blood flow (24, 25).

Enhanced healing of diabetic foot ulcers treated with NNWT also could be associated with the effect of increased warmth on fibroblast growth and proliferation. By using cell culture models it was shown that increased warmth provided by the NNWT system enhanced adult fibroblast proliferation (19) and seemed to reduce the inhibitory effect of chronic wound fluid on newborn fibroblast growth (16).

Infections are a frequent problem in patients with diabetic foot ulcers (26). Concerns exist that the local warm and moist environment provided with NNWT may increase the incidence of wound infection and even spread rather than control infection. In our limited experience with 10 patients treated with NNWT to date we have not seen increased infection rates. Interestingly, researchers feel that applying heat could be an effective method of treating infected tissues (10, 15). Although Rabkin and Hunt (10) showed that local heat increases oxygen tension in wounds, Knighton et

al. showed that increased concentrations of inspired oxygen can control intradermal infections (27). The proposed mechanism for this improved control of infections has been related to in vitro studies in which increased oxygen tension environments improve oxidative killing by polymorphonuclear cells (28).

It appears that elevated temperatures improve neutrophil function. By using in vitro models, Johansen et al. (29) have shown that an increase in temperature from 37°C to 40°C produced increased neutrophil bactericidal activity against the most common wound pathogen *Staphylococcus aureus*. Lee et al., by using an ischemic infected skin flap model in sheep, showed that warming the wound with radiant heat therapy significantly reduced the bacterial burden and controlled infection (15).

Most are in agreement that the key to healing neuropathic diabetic foot ulcers in patients with adequate arterial circulation is successful off-loading of pressure and shearing forces. The application of the NNWT system 3 times daily combined with the use of the donut-shape, foam wound cover may assist in providing some pressure relief and may even assist in patient compliance.

Normally, the wound cover in patients receiving NNWT is changed once daily. In larger, more exudative wounds, skin maceration may occur and the wound cover should be changed more frequently.

Summary

The results of this interim analysis suggest that NNWT may accelerate the healing of diabetic foot ulcers. Further study in a greater patient population is necessary to evaluate the efficacy of this device fully and provide additional information on whether local warmth can reduce the incidence of infection. Based on our limited experience it appears that NNWT is safe and easy to use.

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